REMARKS

The Applicants appreciate the Examiner's thorough examination of the subject application and the indication that claims 15-18 are in a condition for allowance. Applicants request reconsideration of the subject application based on the following remarks.

Claims 9, 10, 12, 14-24 are pending in the application. Claims 9, 10, and 12 have been amended, claim 11 has been cancelled and new claims 19-24 have been introduced. Support for the amendments can be found throughout the specification as filed.

Claims 9-12 and 14 were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Hirai et al. [JP 04139172].

The rejection is traversed.

Applicant respectfully submits that the claims 9-12 and 14, as presented in the amendment filed September 16, 2003 are patentable over Hirai for at least the reasons presented therein. However, in the interest of expediting prosecution, claims 9, 10, and 12 have been amended and claim 11 cancelled. Applicants reserve the right to pursue the cancelled subject matter in this or a subsequent application. Claims 9 and 10, as presently amended, provide compounds of Formula I or IA in which Het or Py are 2,4-disubstituted-6-alkyl-pyridin-3-yl residues, wherein each substituent is a lower alkoxy group having between 1 and 6 carbon atoms or a lower alkylthio group having between 1 and 6 carbon atoms.

As the reference is understood, Hirai does not teach or suggest compounds of Formula I in which Het is a 2,4-disubstituted-6-alkyl-pyridin-3-yl residue or a compound of Formula IA in which Py is a 2,4-disubstituted-6-alkyl-pyridin-3-yl residue not withstanding the disclosure of certain compounds in which R^6 is a substituted pyridine (compounds 71, 72, and 77). More

particularly, Hirai does not teach or suggest compounds in which Het or Py is a 2,4-(alkylthio)-6-alkyl-pyridin-3-yl residue or more particularly a Formula I in which Het is a 2,4-(alkylthio)-6-methyl-pyridin-3-yl residue.

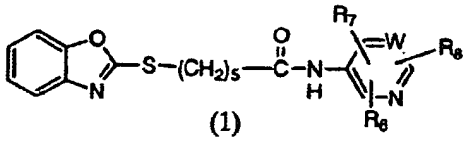
Hirai teaches three compounds having a heteroaromatic residue at the R^6 position, e.g., compounds 71, 72, and 77. None of the compounds recited by Hirai have a pyridine ring substituted with an alkyl group and two substituents selected from alkylthio or alkoxy. That is, Hirai fails to disclose or suggest any compounds in which R^6 is a 2,4-disubstituted-6-methyl-pyridin-3-yl group. More particularly, Hirai neither discloses nor suggests compounds in which R^6 is 2,4-disubstituted-6-methyl-3-pyridyl group or 4,6-disubstituted-2-methyl-5-pyrimidyl group wherein the substituents are lower alkoxy or lower thioalkyl having between 1 and 6 carbon atoms.

As the teachings of Hirai are understood, the biological activity of the compounds disclosed therein is not particularly dependent upon the nature of the R^6 substituent. Thus, the activity is also not effected if these groups are further substituted (See the table of IC_{50} in Hirai).

Applicants have surprisingly discovered that the ACAT inhibitory activity of compounds of Formula I and IA is dependent upon the substitution pattern of the Het or Py pyridine ring. Moreover, Applicants have discovered that the identity of the substituents on the pyridine ring affects ACAT inhibitory activity.

The present inventors conducted the tests of ACAT inhibitory activity of the compounds (1) using microsome ACAT which is derived from arterial walls. The results of a structure-activity relationship study on changes in ACAT activity with variations in pyridine substituents are presented in Table 1. The compounds of the Examples 18, 27, 36 and 88, wherein alkylthio group (methylthio group, ethylthio group and isopropylthio group) and methyl group as

substituents are introduced in the two ortho-position and the para-position in the pyridine part, showed the great ACAT inhibitory activity



(1)

Table 1 ACAT Inhibitory Activity□J774A1 cell□

	Compound No.	R_6	R_7	R_8	W	IC50(nM)	IC50/ IC50 (Ex. 18)
Example 1	5	2-SMe	H	H	=CH-	10200	126
Example 10	455	2-SMe	H	6-Me	=CH-	3400	42
Example 42	365	2-SMe	H	6-OMe	=CH-	>10000	>123
Example 9	275	2-SMe	H	6-sMe	=CH-	3300	41
Example 41	155	2-SMe	4-Me	H	=CH-	510	6.3
Example 18	785	2-SMe	4-SMe	6-Me	=CH-	81	1
Example 27	815	2-SEt	4-SEt	6-Me	=CH-	120	1.5
Example 36	845	2-SPr-i	4-SPr-i	6-Me	=CH-	100	1.2
Reference Example		H	4-Me	6-SMe	=CH-	4300	53

As mentioned in the above, Hirai does not disclose compounds of the claimed invention in which the Het or Py pyridine ring as a two alkylthio substituents at the 2 and 4 position and a methyl residue at the 6 position. Further Hirai neither teaches nor suggests that such compounds would exhibit desirable ACAT inhibitory activity.

Thus, for at least the reasons discussed herein the subgeneric structures of claims 9 and 10 would not have been obvious to one of ordinary skill in the art based on the generic disclosure of Hirai and the absence of structurally related exemplary compounds within the broad genus. The Examiner's attention is further drawn to the MPEP 2144.08 which provides guidelines for determining obviousness of species when prior art teaches a genus. Therefore the claims as presently amended are patentable over Hirai for at least the reasons discussed herein. Applicants request withdrawal of the rejections and reconsideration of the application.

Although it is not believed that any additional fees are needed to consider this submission, the Examiner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

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